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Abstract

Introduction: It can be difficult to distinguish between a second primary and a metastasis in patients with lung cancer who have more than one pulmonary site of cancer.
Methods: A systematic review of the literature was conducted by a subcommittee of the IASLC Staging and Prognostic Factors Committee to develop recommendations to identify second primary lung cancers. The process entailed review of knowledge relating to the mechanism of metastasis, determination of clonality, and outcomes of patients with resected tumors.
Results: It is easier to identify that two tumors are different; finding similarities does not establish that they are the same. For example, the majority of second primary lung cancers are of the same histotype. Few criteria are reliable by themselves; these include different histologic cancer types or matching DNA breakpoints by sequencing, and a comprehensive histologic assessment of resected specimens. Characteristics that are suggestive but associated with potential misclassification include the presence or absence of biomarkers, imaging characteristics, and the presence or absence of nodal involvement.
Conclusion: Clinical and pathologic (i.e. after resection) criteria are presented to identify 2 foci as separate primary lung cancers vs a metastasis. Few features are definitive; many commonly used characteristics are suggestive but associated with a substantial rate of misclassification. Careful review by a multidisciplinary tumor board, considering all available information, is recommended.

Introduction

An increasing number of lung cancers exhibit 2 (or more) malignant pulmonary lesions (15% of surgical patients in a recent large series).[1,2] There is ambiguity in the stage classification of such tumors, and interpretation of how to classify them varies markedly.[3,4] More importantly, it is unclear how to think conceptually about the nature of these lesions, and how to manage the patients.

This paper is a review of pertinent data addressing this scenario, in order to establish a basis for classification of such tumors in the 8th edition of the stage classification system. How to manage these patients is beyond the scope of this paper.

To address how to distinguish a second primary lung cancer from a pulmonary (oligo)metastasis, 3 approaches were chosen. First, we examined current data on the mechanism of metastasis. Second, we reviewed data regarding identification of a single or separate lineage (clonality) -- whatever the mechanism of metastasis might be. Finally, we examined outcomes; specifically, which scenarios are associated with high cure rates (or subsequent disseminated metastases) after definitive local therapy. Considering everything together, we formulated criteria to classify 2 synchronous malignant pulmonary lesions as separate primary cancers or as metastatic from one another.

Methods

The International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee (SPFC) is charged with developing proposals for revision of the stage classification of

lung cancer. To provide greater clarity and consistency in classification of patients with more than one malignant pulmonary lesion, the SPFC appointed an international multidisciplinary subcommittee (the authors of this paper). The full scope of this effort is reported elsewhere;[5-7] however, a fundamental issue is to distinguish whether tumors are separate or related to each other. This specific topic is the focus of this paper.

The multiple lesions subcommittee carried out a systematic search with a methodologist's help for relevant literature from 1995-2015, building on a prior systematic review of patients with multiple tumor lesions conducted by the American College of Chest Physicians (ACCP) for the Lung Cancer Guidelines (3rd edition).[8,9] Reference lists of identified articles were also examined, and each paper in the ACCP review was revisited to ensure appropriate categorization and data abstraction. For the process of metastasis, articles were limited to review articles from 2000-2015. The Population, Intervention, Comparator and Outcomes (PICO) questions, search, results, and inclusion and exclusion criteria are available on request.

The identified evidence was reviewed, interpreted and summarized by the subcommittee through an iterative process. Successive drafts were discussed and circulated for revision. The paper was then sent for critical review to an extended workgroup of individuals with particular interest and expertise in this topic (appendix). The refined paper then underwent further review and eventual endorsement by the entire SPFC.

The Process of Metastasis

Over 85 years ago James Ewing proposed that metastatic dissemination occurs by purely mechanical factors determined by the anatomical structure of the vascular and lymphatic system.[10] This concept was based on a speculative rationale, but was countered by the observation that different primary tumors exhibit a predilection for particular metastatic sites.[11,12] Nevertheless, this simple physical concept of metastasis remains widely pervasive, and terms based on this idea (hematogenous, lymphatic metastases) are still in common use. "Aerogenous" dissemination via the airways was suggested >60 years ago,[13] implying dissemination via airways. The term "intrapulmonary metastasis" has also been used in the context of ≥2 malignant pulmonary lesions and no other sites of cancer (without clarity of how such intrapulmonary dissemination might occur). Recently, the term "spread through air spaces" (STAS) has been introduced,[14,15] but this describes an observation under the microscope immediately adjacent to the tumor.

Knowledge of the process of metastasis has progressed dramatically. The data demonstrates this is an intricate multistep process.[16,17] Evidence indicates that key genetic lesions that permit metastasis are an early event, consistently present in both localized and disseminated tumors.[18] During the process of metastasis the cancer cell is transformed into different phenotypes. Tumor cells exhibit plasticity, meaning they change, including their morphologic characteristics, as they undergo epithelial to mesenchymal transition during the multistep invasion-dissemination process (invasion, intravasation, migration, survival in the circulation), and then likely undergo mesenchymal to epithelial re-differentiation as the extravasation-colonization-metastasis-formation process continues.[16-18]

The various steps are influenced not only by tumor-cell-intrinsic genetic and epigenetic determinants but also a complex array of tumor-host-interactions at both the primary and metastatic sites.[16-18] Tumor cells are present simultaneously in many different forms – at the primary site, as circulating tumor cells and in metastatic sites; furthermore, these various states consist of heterogeneous subpopulations with different gene expression, host-tumor interactions and potential biologic behavior. Circulating tumor cells can be detected frequently in early stage lung cancer – in fact, even before evidence of invasion at the primary site; yet the vast majority (99.98%) do not survive to become distant metastases.[17,19] Disseminated tumor cells exist within permissive niches, often remaining for a long time in a dormant state, but then exit this state and actively grow. In addition, there appears to be a complex dynamic flow of tumor cells between the primary site, circulating cells, metastatic niches, overt metastases and back to the primary site. All of this is influenced by multiple pathways, cell signaling,

tissue microenvironment characteristics, and pressures mediated by growth factors and cytokines selecting certain subpopulations (e.g. hypoxia, immune interactions, chemotherapy etc.).

Additionally, multiple components of the microenvironment steer the metastatic process. Angiogenesis, a major hallmark of cancer, represents activation and proliferation of endothelial cells due to tumor cell hypoxia.[20] Neovascularization allows recruitment of inflammatory and immune cells in the stroma, as well as the invasion and circulation of tumor cells.[21] However, tumor cells hamper activation of immune response through multiple mechanisms, leading to a failure of immunosurveillance.[22]

The amount of data as well as the complexity of the process of metastasis is impressive. Many pieces are still unclear, e.g. the relative impact of various processes and factors governing their rise and fall in importance during the course of the disease. However, the evidence indicates that the process is complex and simple physical transport of a cancer cell via the lymphatics, bloodstream or airways is a grossly inadequate oversimplification.

Section Summary

The concept that metastasis is determined primarily by physical channels for movement of a malignant cell from one site to another is a historic, speculative hypothesis. While this concept can explain some observations, it fails to explain others. More importantly, the scientific evidence demonstrates that a purely physical mechanism is not the primary factor determining metastatic behavior. The terms lymphatic and hematogenous spread are an oversimplification that inhibits consideration of the multistep process of metastasis as it is currently understood.

The actual process of metastasis is too complex to be used to identify which lesions are separate tumors and which have arisen from one another. We conclude that a speculative mechanism of metastasis should not be used to categorize 2 pulmonary lesions.

Establishing a Single or Separate Lineage

Background

Are there tumor characteristics that define 2 lesions as having developed separately vs having arisen together and thus being related? This question requires a “gold standard” that defines separate or related, against which prediction by particular characteristics can be compared; however, no such standard exists.

Patients with widespread metastases are a reasonable clinically-defined cohort with foci of cancer that are related. How well particular characteristics predict a single lineage in this setting is a surrogate for how well such characteristics might identify single lineage in a patient with ≥2 malignant pulmonary lesions (and no other distant metastases). A reasonable definition of unrelated lung cancers are metachronous cancers – ideally, widely separated in time (e.g. >5 years). However, such details are not explicitly reported in published studies.

Comparison of Primary and Metastatic Foci in Patients with Obvious Metastatic Dissemination

Histologic Appearance

It is widely accepted that the histologic appearance of metastases mirrors that of the primary tumor, although sometimes metastases are less well differentiated. Biopsy of a metastasis is considered adequate to establish a diagnosis, and the morphologic appearance is used to define the organ of origin. Although no recent papers address how reliably morphologic appearance is conserved, there are no published reports of a discrepancy. It seems reasonable to accept that the morphology of metastases matches that of the primary site; this implies that a morphologically different appearance is reasonable evidence that two tumors are unrelated.

However, our knowledge of mechanisms that control histologic appearance may be rudimentary. Tumors can change their appearance from one histotype to another. For example, after treatment with an EGFR inhibitor, adenocarcinomas can change their appearance to that of small cell (and back again).[23] In

the laboratory, depending on the culture medium used during early propagation, human mammary cells can be transformed into either a squamous cell carcinoma or an adenocarcinoma.[18,24] Nevertheless, the widespread consistent clinical observation is that morphology is maintained for a given cancer across all sites of growth.

Biomarker pattern:

Genomic analysis of lung cancer led to the identification, among numerous other molecular alterations, of specific mutations that are necessary and sufficient to drive tumor formation and maintenance.[25] These "driver mutations" occur primarily in genes that encode signaling proteins critical for cellular proliferation and survival. Expression of these single mutant oncogenes drives growth, even without other alterations. On the other hand, a hallmark of cancer is genomic instability leading to an increasing number of mutations. However, these "passenger mutations" typically have unknown significance for the growth of tumors, but may indicate a specific developmental lineage within heterogeneous tumors.[26]

In breast cancer, frequent discordance (5-50%) of common biomarkers (ER, PR and HER2) between the primary tumor and metastatic sites is reported.[27] In lung cancer a recent review noted discordance between primary and metastatic sites of 0-38% for an EGFR mutation, and 23-33% for EGFR by FISH.[27] Numerous other studies (Figure 1) report a substantial rate of discordance (~25%, range 12-45%) between primary and metastatic sites of lung cancer for driver mutations (EGFR, KRAS, p53);[28-38] only one study of 6 patients found no discordance.[39] Similarly, sampling of 50-60 different areas in 21 resected EGFR-mutated lung cancers found mixtures of EGFR mutated and non-mutated cells in 29% of the samples.[40] However, discordance might be explained by technical variability, assay sensitivity, size of specimens, tumor cell content, storage issues, and variable sensitivity of genotyping methods. A carefully done study using multiple controls found no discordance between primary and metastatic sites in 137 lung adenocarcinomas, and no heterogeneity among 3 different sampled areas of a tumor in 50 patients and among 100 different areas in 5 patients.[41] Another detailed analysis using multiplex sequencing found only 7% discordance between primary and metastatic sites for lung cancer driver mutations, but ~40% for somatic alterations (i.e. passenger mutations).[42] Discordance in ALK rearrangements between primary tumors and metastases has also been reported.[43]

Comparison of Foci in Patients with Clearly Separate Tumors

Histologic Appearance

The majority of 2nd primary lung cancers are consistently reported as being the same major histotype (e.g. adenocarcinoma, squamous cell carcinoma).[9,44-66] Generally good outcomes are observed, suggesting the assessment as 2 separate primary cancers was correct. Furthermore, there is no survival difference in 2nd primary cancers with the same vs a different cell type.[9,45-49,55,57-61,63,65-69,70] Rarely has a trend to better survival been observed when the histotypes are different.[62,71]

Therefore, the finding that two (otherwise seemingly separate) tumors are of the same cell type is not proof that these are a single tumor. Whatever etiologic factors are involved in a patient might be expected to lead to the same histotype, potentially explaining the fact that most often both tumors are the same cell type.

Biomarker pattern:

There is little data regarding how often metachronous 2nd primary lung cancers exhibit the same genetic mutation. One study of 75 evaluable patients found that 33% of metachronous 2nd primary lung cancers had matching EGFR and/or p53 mutations as the 1st primary lung cancer.[72] Matching mutations could simply reflect the high prevalence of such mutations or the impact of similar etiologic factors. In addition, several studies have shown that driver mutations are frequently (7-43%) present in normal lung tissues of patients with lung cancer.[73-75] A germline EGFR mutation that confers a predisposition to similar familial lung cancers across multiple generations has also been demonstrated.[76-78] Thus, finding the same gene mutation does not prove that 2 lung cancers arose from the same clone.

Potential Criteria to Define Lineage of 2 Malignant Lung Lesions

Histologic Appearance

Histologic type:

Because histologic appearance is conserved when widely metastatic, it seems very unlikely that it wouldn't be conserved in an oligometastasis. This rationale argues that we can be confident that lesions of different tumor types have developed independently.

However, 2 lesions of the same major histotype in a given patient does not prove they arose from a single source (indeed, it is the most common presentation of separate primary lung cancers). Two lesions being of the same histologic type should be viewed as necessary but not sufficient to establish a single lineage.

A recent systematic review and metaanalysis found an interobserver agreement rate on NSCLC histotype in resected specimens of 67-90% (3022 cases total).[79] A study based on 1032 biopsy specimens noted agreement in 81% of cases (no immunostains were used).[80] Cell type diagnosed by cytology was concordant with histology in 87% of 158 cases in another study (excluding inconclusive cases).[81] However, these studies were conducted prior to the 2015 revisions in the WHO classification.[82]

Histologic subtype:

A more detailed assessment has been proposed, involving evaluation of the histologic subtype, the relative proportion of subtypes, grade, cytologic and stromal features (Figure 2).[83] In an assessment of 20 patients with 42 multiple lesions (both synchronous and metachronous) the comprehensive histologic assessment was concordant with a detailed molecular assessment (5-gene mutation panel and CGH) in 91%. Furthermore, patients classified as having separate cancers by the comprehensive histologic assessment exhibited good survival, and those classified as similar tumors had poor survival after resection; the detailed histologic assessment predicted survival better than either molecular or Martini-Melamed (M&M) criteria.[83] A study involving a similar approach found 91% concordance of the detailed histologic assessment with a detailed molecular evaluation; survival in the 12 study patients was not assessed.[84] Another study[66] observed equal survival for node-negative synchronous adenocarcinomas whether classified as the same or different by histologic subtype assessment (n=30 vs 48, 5-year OS 61% vs 69%, p=0.5, respectively). However, no detailed assessment was performed (i.e. percentages of each subtype, stromal, cytologic or nuclear characteristics). Furthermore, reproducibility in subtyping adenocarcinomas and poorly differentiated NSCLC is moderate, likely due to heterogeneity.[85,86]

Details of how a comprehensive histologic assessment is done may be important: the comprehensive histologic assessment did not perform well in banked frozen tissue samples, being discordant with paraffin embedded tissue in 17% and not evaluable in another 8%.[83] This means the comprehensive histologic assessment is primarily applicable to resected patients (after treatment decisions have been made). It has not been assessed in small-biopsy specimens or intraoperative frozen section settings.

Supporting a comprehensive histologic assessment as a way to identify tumors as being separate or the same is the general conservation of appearance between primary tumors and (distant) metastases, the correlation with a detailed genomic assessment, and with survival in one study.[83] Furthermore, the comprehensive histologic assessment, (when consistently assessed by 2 reviewers) was concordant with the linage as assessed by CGH in 89% (9/11 patients).[87] Nevertheless, the data on comprehensive histologic assessment is based on a limited number of patients and we lack a gold standard. It may be that a different appearance on detailed assessment is sufficient to define separate primary tumors, but a similar appearance does not necessarily define lesions as metastases.

Genetic Characterization

Many types of genetic characterization are available, each with advantages and limitations. Furthermore, genetic alterations may involve specific mutations, gene amplifications or deletions, and gene fusions or rearrangements. Mutation profiling by PCR sequencing (for specific mutations) and FISH

(for amplification/deletions and fusion/rearrangements) are inexpensive, widely available and feasible in small biopsies, but have limited sensitivity in heterogeneous specimens (i.e. low tumor content). Multiplex genotyping assays have increased sensitivity and allow simultaneous detection of multiple mutations, but are applicable only to pre-specified specific mutations. Multiplex PCR-based massively parallel next-generation sequencing does not require pre-specification but is not applicable to amplification or fusion alterations. Comparative genomic hybridization (CGH) to detect chromosomal aberrations and focal amplification/deletion has become more widely available but requires a relatively large amount of high quality DNA. So-called "third generation" capture-based massively parallel next-generation sequencing has high sensitivity and can rapidly detect all types of genetic alterations, requires less DNA and is applicable to biopsies. This approach can detect thousands of single nucleotide variations (SNV) and rearrangements – and while the same specific SNV mutations (e.g. in EGFR, KRAS genes) are often found in different patients, identical breakpoints in genetic rearrangements have not been detected among different patients.[87,88] Finally whole-exome or whole-genome sequencing has been proposed, but suffers from being expensive, not being applicable for rearrangements, hard to implement in the clinic, and having limited sensitivity as currently available.

Specific Mutations

Many studies assessed particular mutations to define clonality – assuming that a match of a few (1-5) markers defines a single clone whereas a difference defines separate cancers (Supplementary Table S1, Supplemental Digital Content 1).[73,89-92] However, the heterogeneity of marker detection in clearly related tumor deposits (Figure 1) calls for caution. OS after resection can serve as a gold standard; it is striking that studies evaluating survival demonstrated no correlation between clonality defined by specific gene mutations and outcomes (Supplementary Table S1, Supplemental Digital Content 1).[73,90,93] Therefore, it is unclear that either a difference in specific mutations identifies separate primary cancers or that mutations in the same gene defines a single lineage.

Comparative genomic hybridization

Some studies used more sophisticated genomic analysis techniques, often combined with assessment of specific mutations.[1,84] The markedly greater detail assessed suggests these may be more reliable measure of clonality. When comparing such a detailed genomic assessment with evaluation of specific mutations or with a comprehensive histologic assessment (type, subtype, various morphologic features), each technique shows a low level of discordance with the other assessments in 0-25% in small studies (8 and 12 patients),[1,84] and it is not clear that the more sophisticated techniques are best. The survival of patients classified by CGH plus mutational profiling as different tumors showed only a non-significant trend towards better survival than those classified as similar tumors (n=20, p=0.13).[83] Moreover, CGH is complex to integrate in a routine clinical practice, especially on small biopsies, given the need of high amounts of high quality tumor DNA.

Next-generation sequencing

Next-generation DNA sequencing identifies breakpoints in gene rearrangements; to date no duplicate breakpoints have been reported among clearly unrelated tumors (e.g. different patients, different histology tumors), whereas shared breakpoints are common within related tumors (primary and metastatic sites or in multiple biopsies of one site).[87] This technique appears promising to identify lineage;[87] however, there is no gold standard to compare with, and the evaluation is limited to 11 patients.[87] Furthermore, the analysis involves complex management of a bioinformatics algorithm (e.g. to minimize false-positives, false negatives and other errors) and a probability statistic (to estimate the probability of relatedness based on the number of shared breakpoints).[87]

Section Summary

In the setting of obvious metastatic dissemination, the histologic appearance is generally conserved. Thus, it is reasonable to conclude that lesions of different histotypes are 2 separate primary cancers. A more detailed histologic assessment (Figure 2) appears to be useful, although only reported in

a few small studies and without a gold standard that would permit robust assessment. Nevertheless, it seems reasonable to define lesions that are different by a comprehensive histologic assessment as separate primary cancers. This is based on the general conservation of histologic appearance between primary and metastatic sites, and the correlation with survival and with a detailed genomic assessment.

Establishing that 2 lesions are not just similar but actually the same tumor is more difficult. Simple demonstration of the same histotype is not sufficient. It is appealing to consider a comprehensive histologic assessment, but the data regarding this is limited, and probably applies primarily to resected specimens (after a management decision has been made). At this point we conclude that a matching appearance by detailed histologic assessment is best viewed as strongly suggestive that lesions are of a single lineage.

Demonstration of specific driver mutations by widely available PCR sequencing techniques is suggestive but not definitive in establishing relatedness. Reliance on mutation pattern should be tempered by the general prevalence of these mutations and the moderate frequency of discordance between primary and metastatic sites in obviously disseminated disease. Mutation pattern must be considered together with other data (e.g. clinical, radiologic, morphologic).

A detailed genetic assessment, such as CGH may have greater discriminative power, but has been used in only a few small studies. There appears to be some discordance compared with other assessments of tumor relatedness, and correlation with survival is poor. Much more sophisticated techniques such as next-generation sequencing and comparison of exact breakpoints in gene rearrangements is promising; however data is limited, the assessment complex, and at this time is more applicable as a research than a clinical tool. Finally, the demonstration of re-seeding of primary sites from metastatic sites[94] may hamper our ability to compare molecular profiles in multiple cancers.

Patient Outcomes after Treatment

Five-year OS after definitive local therapy is high (~70%) in patients with stage I NSCLC and low (~15%) in those with (oligo)metastatic disease.[95] (We defined definitive local therapy as lobectomy or segmentectomy for stage I NSCLC; the efficacy of wedge resection or stereotactic body radiation therapy [SBRT] is more ambiguous and potentially confounded [e.g. comorbidities, staging, limited margins].) Thus, good or poor OS after resection of 2 pulmonary sites of cancer strongly suggests either synchronous stage I cancers or (oligo)metastatic disease. The absence of a rapid appearance of distant metastases could also distinguish these entities, but this outcome is rarely reported.

However, good outcomes may be seen in indolent tumors regardless of treatment (e.g. adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and poor outcomes may result from factors unrelated to the tumor biology (e.g. comorbidities or not undergoing definitive therapy). Outcomes in patients who are not treated with definitive or effective local therapy are not helpful.

Our systematic review of synchronous lung cancers (Table 1) show that good 5-year survival was achieved (especially for N0 patients). The centers appear to have appropriately identified synchronous primary cancers, but are vague about how this was done. The survival rates have generally improved over time – with some variability, possibly due to selection (e.g. favorable oncologic or physiologic characteristics), inclusion criteria (e.g. incidental, bilateral lesions) resection extent (e.g. rate of pneumonectomy or wedge) or other factors.

Cited Criteria to Distinguish Multiple Primary Lung Cancers from Pulmonary Metastases

The Martini and Melamed (M&M) criteria (Supplementary Table S2, Supplemental Digital Content 1), proposed in 1975, were empirically derived, applied to only 50 patients (18 synchronous), and intended as a clinical management tool rather than a definition of multiple primary cancer.[96] At that time only tumor location and nodal status was available (i.e. no computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging MRI or molecular profiling). The criteria are based primarily on major histotype, an arbitrary time interval for metachronous tumors (2 years) and rationale emanating from a view of metastasis as the physical translocation of a malignant cell (considered

metastasis if in different segments but with carcinoma in lymphatics common to both – seemingly implying retrograde lymphatic migration to the metastatic site?).

The M&M criteria are widely cited as being used (Table 1); however in many studies they seem to have been used loosely, supplemented by clinical judgment. In some series other criteria were used. The ACCP proposed criteria in 2003 that differed only slightly from M&M (Supplementary Table S2, Supplemental Digital Content 1). The 7th edition of TNM classification states "Multiple tumours of similar histological appearance should only be considered to be synchronous primary tumours if in the opinion of the pathologist, based on features such as differences in morphology, immunohistochemistry and/or molecular studies, or in the case of squamous cancers, are associated with carcinoma in situ, they represent differing sub-types of the same histopathological cell type. Such cases should also have no evidence of mediastinal nodal metastases or of nodal metastases within a common nodal drainage."[97-99] Thus, this categorization blends the comprehensive histologic assessment with some features of M&M. However, it only defines pathologic assessment, and does not consider other clinical features (imaging characteristics).

Little formal testing of these criteria has been performed. Girard et al compared differentiation of multiple primaries and metastases according to M&M against comprehensive histologic assessment and against molecular characterization in 20 patients (42 tumors).[83] There were significant discrepancies in the categorization by each method (20% different by molecular characterization and 12% by comprehensive histologic assessment vs M&M), The authors used survival as a gold standard; all underwent curative-intent resection (but nodal status was not reported). Significantly better survival for patients categorized as separate primary vs metastasis was only found using the comprehensive histologic assessment; both M&M and molecular characterization demonstrated only a non-significant trend. Of note, although M&M criteria are cited as having been used, 15% of patients were selected for curative-intent resection despite M&M classification as metastatic.[83]

Section Summary

Published studies only vaguely define patient characteristics and selection criteria for curative treatment. Nevertheless, the observed OS is similar to what is expected for separate primary cancers. The M&M criteria are most commonly cited, but appear to have been supplemented by clinical judgment; the retrospective nature and lack of detail hampers assessment of the selection criteria. The M&M criteria have not performed well when compared against a comprehensive histologic assessment. Nevertheless, such a comprehensive assessment is only possible after resection. Thus, data from outcomes provides limited specific information to define separate primary lung cancer vs metastases.

Proposed Criteria to Distinguish Synchronous Second Primary Lung Cancer

Taking all the information gleaned from this review together, criteria were developed for clinical and pathologic identification of synchronous separate vs related pulmonary tumors (Table 2, 3). We suggest that for clinical definition, all available information be considered, including imaging, biopsy and clinical features. Most factors can only be viewed as suggestive; an adequate biopsy showing different histotypes is the only feature that by itself defines separate primary cancers (but the converse is only suggestive!).

For pathologic definition, a comprehensive histologic assessment can be viewed as definitive if it demonstrates that tumors are different but is only suggestive if they appear similar. The pattern of biomarker alterations should only be viewed as suggestive, whether similar or different. In all cases, the pathologic information should be supplemented with available clinical information.

Tumors should be categorized as separate primary cancers or metastases according to the preponderance of the evidence. A quantified approach is not possible (e.g. the number of suggestive factors) because the strength of a particular factor must be weighed (e.g. the extent of available prior imaging, biopsy tissue quality, degree of imaging or histologic similarity). Ideally, the decision of how to

categorize 2 lesions in a patient should be made with multidisciplinary input upon considering all available information (i.e. a tumor board).[9]

Discussion

This paper represents an expert consensus based on a comprehensive literature review of available data to guide categorization of 2 synchronous pulmonary tumors in a patient as being separate primary cancers or related to one another. This is a relatively common clinical issue, and currently there is great variability in how patients are classified.[3,4] This not only creates potential harm from inappropriate management, but also thwarts the ability to carry out research based on recorded classification.

A review of what is known about the mechanism of metastasis reveals extensive evidence demonstrating a complex process. Rationale based solely on a physical route of dissemination of cancer cells ignores the myriad of factors that control the complex process of metastasis. Terms such as lymphatic or hematogenous metastasis are gross oversimplifications, and classification or management of patients based on simplistic concepts is not justified.

A reliable assessment that tumors are unrelated can be made if they have a different histotype or appear different on a detailed histologic assessment of tumor subtypes and stromal features. However, two lesions having the same histology does not prove tumors are related; most separate primary cancers are of the same histotype, and clonality studies also suggest that most often they are not related. Classifying tumors as related should be done carefully, taking into account the aggregate of available information. When there is doubt, it may be better to regard the tumors as separate, given the evidence reviewed in this paper.

We must also be careful about relying on biomarkers. Although they can suggest that tumors are separate or related, the incidence of discordance in clearly related lesions and concordance in clearly unrelated lesions is relatively high. Test sensitivity, tissue quality and other factors may account for much of the discrepancy. More sophisticated methods may become broadly available in the future. However, at present, mutational profiling should not be considered definitive.

The M&M schema has been a useful starting point, but does not have a solid foundation; it is mainly empirically derived, based on outdated concepts and has not performed well when compared to newer approaches. It appears to be best to replace this with the criteria suggested here. Unfortunately few criteria can be proposed that are definitive by themselves, and generally a decision must be made using the aggregate of all information available.

We acknowledge that no data is available that quantifies many of the relative criteria to consider in making a clinical judgment that 2 lesions are separate primary or metastatic lesions (e.g. radiographic metabolic characteristics, growth patterns or nodal status). Nevertheless, the published experience demonstrates that clinical judgment used to identify patients as having synchronous primary tumors resulted in reasonably good outcomes.

We have focused on patients with two synchronous lesions; a metachronous presentation presents considerations that are beyond the scope of this paper. Various time intervals between tumors have been suggested (Table S2), but these are arbitrary. We suggest that the data and criteria proposed here for synchronous tumors can also guide classification of metachronous tumors, supplemented by additional clinical judgment arising from consideration of the time interval and stage of the first tumor.

If the proposed criteria and clinical judgment suggest two lesions are unrelated, they should be classified as separate primary cancers and each one staged and managed individually.[6] If they are categorized as related, the patient should most often be classified as having an additional tumor nodule as is described in detail elsewhere.[5,6] The exception to this are patients that have multiple nodules with ground glass features (or AIS, MIA or lepidic predominant adenocarcinoma (LPA) on histology). These patients should be classified as having multifocal lung cancer.[6,7]

From a clinical standpoint, the expertise for comprehensive histologic assessment, as well as the availability of mutation profiling and genomic techniques is not yet widely available. The need for a significant amount of tissue both to analyze the morphology and to extract sufficient tumor DNA for

molecular techniques makes the relevance of those approaches uncertain. Distinguishing primary tumors from metastases is most important prior to therapeutic intervention than after resection. Unfortunately, limited data is available regarding the imaging or metabolic features of multiple lung tumors. Nevertheless, clinical judgment appears to have worked well in identifying appropriate patients for curative-intent treatment as demonstrated by reported outcomes

The *process* of clinical evaluation of patients is outside the scope of this paper; the ACCP Clinical Guideline recommends careful imaging and invasive evaluation for occult distant and mediastinal metastases for patients with synchronous separate primary lung cancers as well as for patients with additional tumor nodules.[9,100] Treatment recommendations are also not part of this review; however the data presented here suggests that in properly selected patients curative-intent treatment is associated with good outcomes.

Further research is needed to test and refine the proposed criteria, but the lack of a gold standard that easily and reliably identifies separate vs related tumors in the lung makes this difficult. Prospective studies are needed to assess how well the proposed criteria identify patients with good outcomes. We hope that this paper is helpful not only in categorization of patients as well as in stimulating further research.

Conclusion

It is easier to establish that 2 pulmonary foci of cancer are separate primary tumors than that they are metastatic from one another (for example, most second primary lung cancers are of the same histotype). Few features are sufficiently reliable by themselves, such as different histologic type, differences by a comprehensive histologic assessment or resected specimens or matching breakpoints by DNA sequencing. Most criteria can be suggestive, but are associated with potential misclassification. These include biomarker patterns, imaging characteristics or the presence or absence of nodal involvement. The fact that generally only biopsy specimens are available at the time of clinical decision-making further adds to the uncertainty and difficulty of the assessment. A constellation of factors is better than any single factor; it is best to make a determination of separate primary vs. metastatic lesions through collective judgment of a multidisciplinary tumor board after taking into account all of the available information.

APPENDIX

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Tables

Table 1: Survival of Patients with Synchronous Second Primary Lung Cancers

First Author	Year	N	Definition	% incidental[a]	% resected	% limited resection[b]	% Op mort	% 5- year Survival		% 5-year Survival by Histotype		
								All	pI	same	diff	p
Yu[66]	2013	97	Girard	-	100	51	0	70	70[c]	65	74	.3
Zuin[106]	2013	23	M&M?	-	100	-	-	40	-	-	-	-
Shah[d 59]	2012	47	-[d]	0	100	83	2	29	-	23	40	.9
Fabian[60]	2011	67	-	-	100	60	2	53	-	49	42	.9
Jung[70]	2011	32	M&M	3	100	50	9	61	69	100	36	,003
Kocaturk[62]	2011	26	unclear	-	92	38	8	50	-	25	78	.2
Finley[61]	2010	175	Girard	42	100	27	1	52	64[e]	(67)[f]	(50)[f]	>.05
Voltolini[65]	2010	50	-	0	>90	65	7	31	57	34	33	.6
Riquet[57]	2008	118	unclear	-	100	16	5	26	-	33	20	.4
Rostad[58]	2008	94	unclear	79	100	16	9	33	-	No diff		.3
De Leyn[d 55]	2008	36	-[d]	-	100	72	3	38	-	31	45	.3
Trousse[107]	2007	125	M&M?	-	100	14	11	34	51	-	-	-
Chang[108]	2007	92	-	-	100	11	1	35	53	-	-	-
Vansteenkiste[109]	2001	35	unclear	-	100	23	9	33	-	-	-	-
Van Rens[110]	2000	85	M&M?	32	100	13	14	20	23	No diff		-
Okada[50]	1998	28	M&M?	39	96	7	0	70	79[g]	-	-	-
Antakli[51]	1995	26	Antakli	19	92	42	-	5	-	-	-	-
Average[h]				**27**		**37**	**5**	**40**	**58**	**45**	**46**	

Inclusion criteria were studies from December 1995-April 2015 of ≥ 20 patients with synchronous second primary lung cancers reporting survival data.

Antakli = Criteria proposed by Antakli; Diff = difference; Girard = M&M plus detailed histologic evaluation similar to Girard; M&M = Martini and Melamed criteria; M&M? = Martini and Melamed criteria cited but do not appear to have been strictly adhered to; Op Mort = operative mortality; pI = pathologic stage I

[a]Percentage found incidentally at time of resection.

[b]Percentage of patients who underwent wedge resection or segmentectomy.

[c]includes 8% T3N0M0 for largest tumor

[d]bilateral tumors only

[e]Stage Ia only.

[f]3 year survival, excluded from average calculation

[g]Stages I and II.

[h]Excluding values in parentheses.

Table 2: Clinical Criteria for Separate vs Related Pulmonary Tumors

Clinical Criteria*
Tumors may be considered separate primary tumors if: They are clearly of a different histologic type (e.g. squamous carcinoma and adenocarcinoma)
Tumors may be considered to be arising from a single tumor source if: Matching breakpoints are identified by comparative genomic hybridization (CGH)
Relative arguments that favor separate tumors: Different radiographic appearance or metabolic uptake Different pattern of biomarkers (driver gene mutations) Different rates of growth (if previous imaging is available) Absence of nodal or systemic metastases
Relative arguments that favor a single tumor source: The same radiographic appearance Similar growth patterns (if previous imaging is available) Significant nodal or systemic metastases The same biomarker pattern (and same histotype)
**Note that a comprehensive histologic assessment is not included in clinical staging, as it requires that the entire specimen has been resected.*

Table 3: Pathologic Criteria for Separate vs Related Pulmonary Tumors

Pathologic Criteria (i.e. after resection)*

Tumors may be considered separate primary tumors if:
They are clearly of a different histologic type (e.g. squamous carcinoma and adenocarcinoma)
They are clearly different by a comprehensive histologic assessment (see below)
Squamous carcinomas that have arisen from carcinoma in situ

Tumors may be considered to be arising from a single tumor source if:
Exactly matching breakpoints are identified by comparative genomic hybridization

Relative arguments that favor separate tumors (to be considered together with clinical factors):
Different pattern of biomarkers
Absence of nodal or systemic metastases

Relative arguments that favor a single tumor source (to be considered together with clinical factors):
Matching appearance on comprehensive histologic assessment
The same biomarker pattern
Significant nodal or systemic metastases

**Pathologic information should be supplemented with any clinical information that is available*

Figures

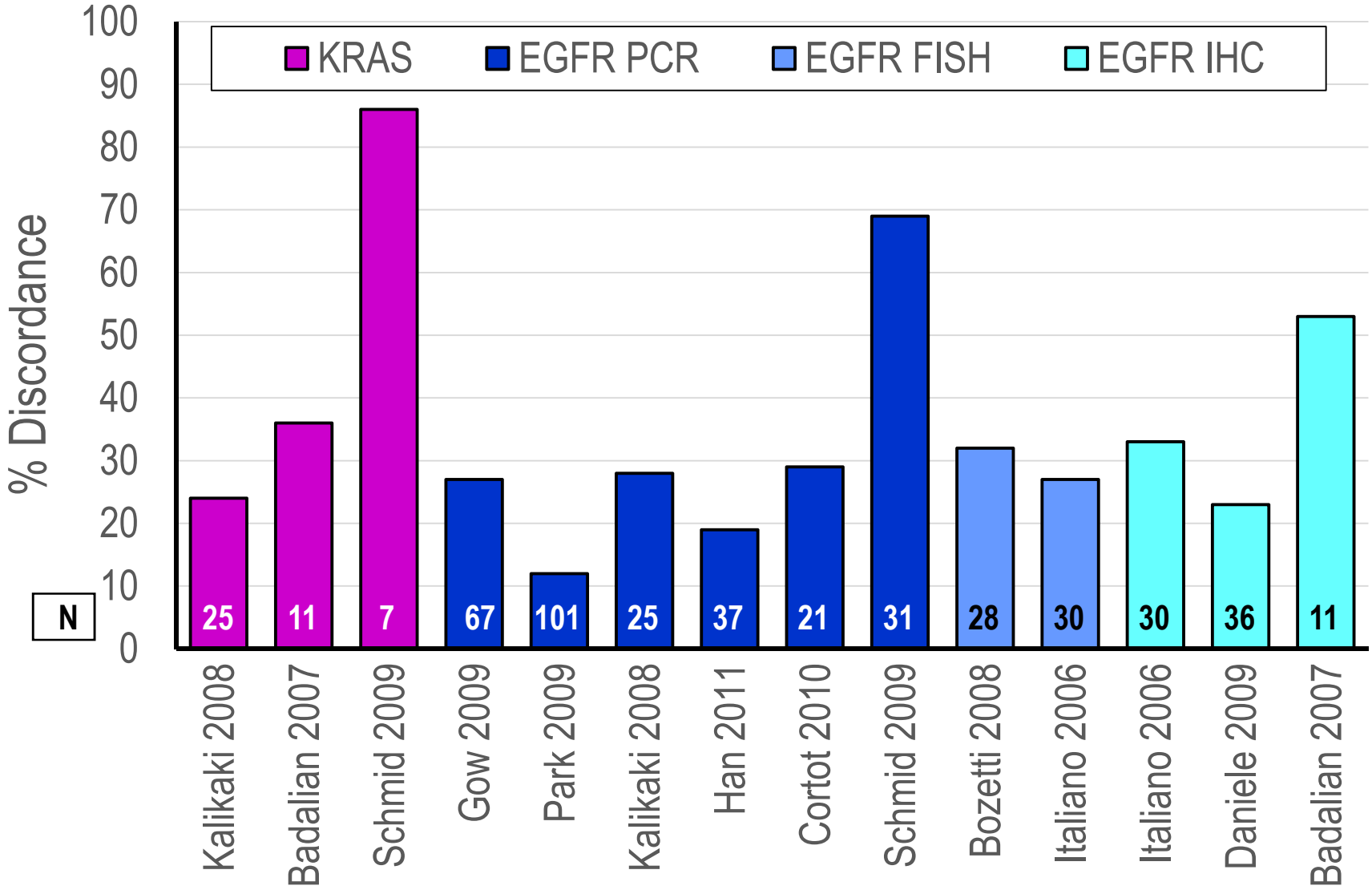
Figure 1: Biomarker Discordance Rates

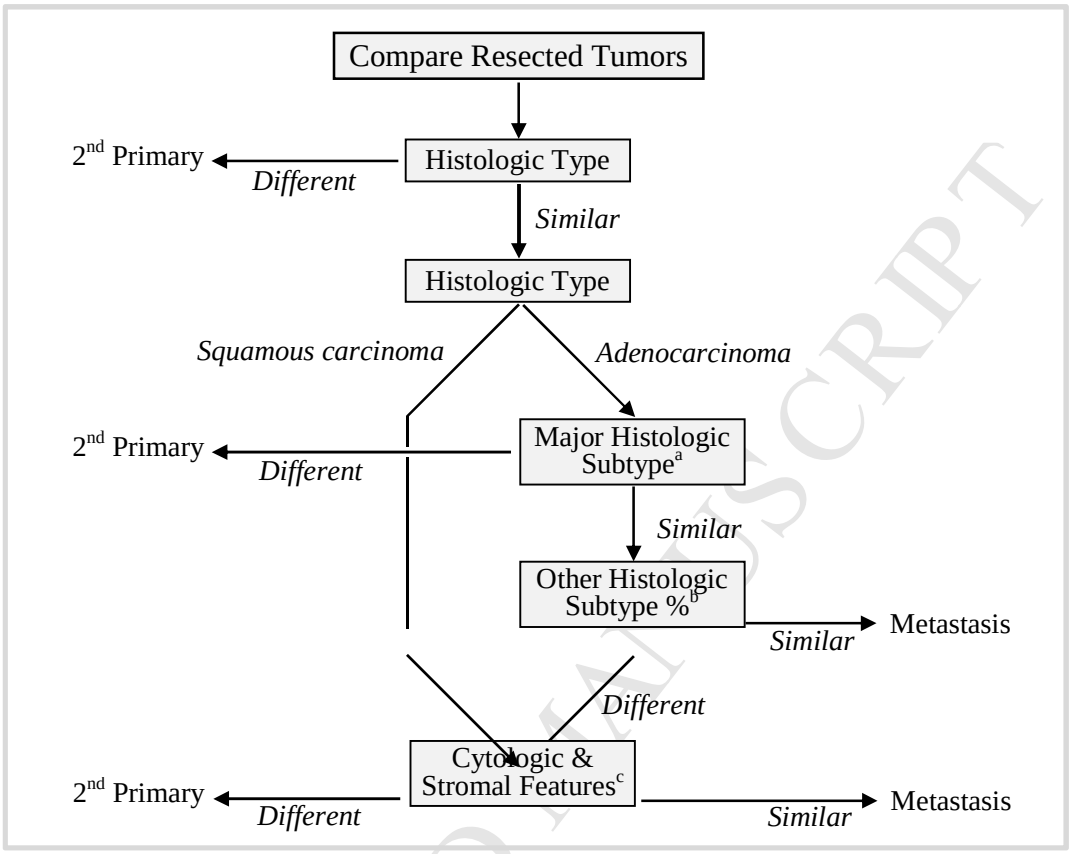
Reported rates of discordance between primary and metastatic sites of lung cancer for various biomarkers. These studies excluded patients who had been treated.

Figure 2: Process of Comprehensive Histologic Assessment

Process of conducting a comprehensive histologic assessment. Adapted from Girard et al.[83]
[a] The predominant subtype is determined
[b] The relative percentage of each histologic subtype is estimated in 10% increments.
[c] Cytologic/stromal features include grade, necrosis, inflammation, lymphoid hyperplasia, desmoplasia or keratinization.

Discordance in Biomarkers between Primary Tumor and Metastatic Site





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